PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 01 February 2001 (01.02.01)	
International application No.: PCT/JP00/04909	Applicant's or agent's file reference: 51-06025WO
International filing date: 24 July 2000 (24.07.00)	Priority date: 26 July 1999 (26.07.99)
Applicant: TAKEMOTO, Hiroshi et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

10 November 2000 (10.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer: J. Zahra Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

(12)特許協力条約に基づいて公開された国際

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2001年2月1日 (01.02.2001)

PCT

(10) 国際公開番号
WO 01/07423 A1

(51) 国際特許分類[7]: C07D 277/34, 277/36, 277/46, 277/60, 275/02, 417/12, 417/14, 513/04, A61K 31/426, 31/425, 31/427, 31/429, 31/4439, 31/4709, 31/4725, A61P 7/04, 43/00

(21) 国際出願番号: PCT/JP00/04909

(22) 国際出願日: 2000年7月24日 (24.07.2000)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:
特願平11/211164 1999年7月26日 (26.07.1999) JP

(71) 出願人 (米国を除く全ての指定国について): 塩野義製薬株式会社 (SHIONOGI & CO., LTD.) [JP/JP]; 〒541-0045 大阪府大阪市中央区道修町3丁目1番8号 Osaka (JP).

(72) 発明者; および
(75) 発明者/出願人 (米国についてのみ): 武本 浩 (TAKEMOTO, Hiroshi) [JP/JP]. 高山正己 (TAKAYAMA, Masami) [JP/JP]. 塩田武司 (SHIOTA, Takeshi) [JP/JP]; 〒553-0002 大阪府大阪市福島区鷺洲5丁目12番4号 塩野義製薬株式会社内 Osaka (JP).

(74) 代理人: 山内秀晃, 外(YAMAUCHI, Hideaki et al.); 〒553-0002 大阪府大阪市福島区鷺洲5丁目12番4号 塩野義製薬株式会社 知的財産部 Osaka (JP).

(81) 指定国 (国内): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

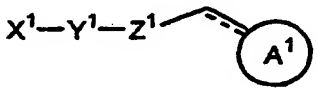
(84) 指定国 (広域): ARIPO 特許 (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:
— 国際調査報告書

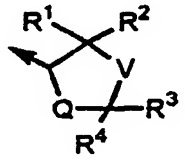
２文字コード及び他の略語については、定期発行される各PCTガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

(54) Title: DRUG COMPOSITIONS EXHIBITING THROMBOPOIETIN AGONISM

(54) 発明の名称: トロンボポエチン受容体アゴニスト作用を有する医薬組成物

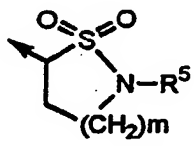


(I)



(II)

または
OR



(III)

(57) Abstract: Drug compositions containing as the active ingredient compounds of general formula (I), prodrugs of the same, pharmaceutically acceptable salts of both, or solvates of them and exhibiting thrombopoietin receptor agonism: wherein X^1 is optionally substituted heteroaryl or the like; Y^1 is $NR^ACO-(CH_2)_{0-2}-$ or the like (wherein R^A is hydrogen or the like); Z^1 is optionally substituted allylene or the like; and A^1 is a ring represented by general formula (II) or (III):

[続葉有]

WO 01/07423 A1

ANNEX (AMENDED SHEETS)

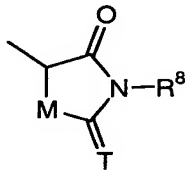
(1st Amendment)

wherein E is $-(CH_2)_{1-3}-$, $-O-CH_2-$, or $-S-CH_2-$; R^6 and R^7 are each independently a hydrogen atom, optionally substituted lower alkyl, carboxy, lower alkyloxycarbonyl, optionally substituted aminocarbonyl, optionally substituted thienyl, or optionally substituted phenyl; R^8 is a hydrogen atom or lower alkyl.

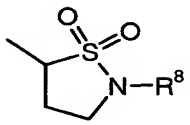
4. A pharmaceutical composition of any one of claims 1 to 3, wherein Y^1 is $-NHCO-$, $-CONH-$, $-NHCH_2-$, or $-NHSO_2-$.

5. A pharmaceutical composition of any one of claims 1 to 4, wherein Z^1 is 1,4-phenylene.

6. A pharmaceutical composition of any one of claims 1 to 6, wherein A^1 is a ring represented by the formula:



or



wherein R^8 is a hydrogen atom or lower alkyl; M is -S-, -O-, $-N(R^c)-$, or $-CH_2-$ (wherein R^c is a hydrogen atom or lower alkyl); T is an oxygen atom or a sulfur atom.

7. A pharmaceutical composition of any one of claims 1 to 6, wherein the broken line represents the presence of a bond.

8.(Amendment) A pharmaceutical composition of any one of claims 1 to 7, which is for for treating or preventing hemopathy accompanied with the unusual number of platelets.

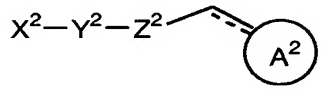
9. A pharmaceutical composition of any one of claims 1 to 7, which is a platelet production modifier.

10. (Amendment) Use of a compound of any one of claims 1 to 7 for preparation of a pharmaceutical composition for treating hemopathy accompanied with the unusual number of platelets.

(1st Amendment)

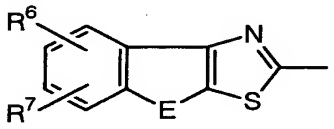
11. (Amendment) A method for treating hemopathy accompanied with the unusual number of platelets of a mammal, including a human, which comprises administration to said mammal of a compound of any one of claims 1 to 7 in a pharmaceutically effective amount.

12. (Amendment) A compound represented by the formula (II)



(II)

wherein X^2 is optionally substituted 5-member heteroaryl or a group represented by the formula:



wherein E is $-(CH_2)_{1-3}-$, $-O-CH_2-$, or $-S-CH_2-$; R^6 and R^7 are each independently a hydrogen atom, optionally substituted lower alkyl, carboxy, lower alkyloxycarbonyl, optionally substituted aminocarbonyl, optionally substituted thienyl, or optionally substituted phenyl;

Y^2 is $-NR^GCO-(CH_2)_{0-2}-$, $-NR^GCO-(CH_2)_{0-2}-W-$, $-NR^GCO-CH=CH-$, $-W-(CH_2)_{1-5}-NR^GCO-(CH_2)_{0-2}-$, $-W-(CH_2)_{1-5}-CONR^G-(CH_2)_{0-2}-$, $-CONR^G-(CH_2)_{0-2}-$, $-(CH_2)_{0-5}-NR^G-SO_2-(CH_2)_{0-5}-$, $-(CH_2)_{0-5}-SO_2-NR^G-(CH_2)_{0-5}-$, $-NR^G-(CH_2)_{0-2}-$, $-NR^G-CO-NR^G-$, $-NR^G-CS-NR^G-$, $-N=C(-SR^G)-NR^G-$, $-NR^GCSNR^GCO-$, $-N=C(-SR^G)-NR^GCO-$, $-NR^G-(CH_2)_{1-2}-NR^G-CO-$, $-NR^GCONR^GNR^FCO-$, or $-N=C(-NR^GR^G)-NR^G-CO-$,

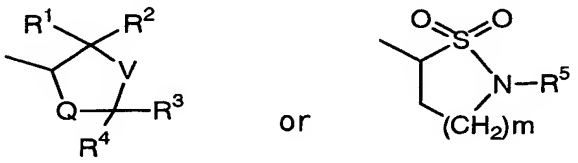
wherein R^G is each independently a hydrogen atom or optionally substituted lower alkyl, R^F is a hydrogen atom or optionally substituted aryl, W is an oxygen atom or a sulfur atom;

Z^2 is optionally substituted phenylene, optionally substituted 2,5-pyridine-

(1st Amendment)

diyl, optionally substituted 2,5-thiophene-diyl, or optionally substituted 2,5-furan-diyl;

A^2 is a ring represented by the formula:



wherein R^1 and R^2 are both hydrogen atoms or taken together may form an oxygen atom or a sulfur atom; R^3 and R^4 are both hydrogen atoms or taken together may form an oxygen atom or a sulfur atom; R^5 is a hydrogen atom or lower alkyl; Q and V are each independently -O-, -S-, -NR^B- (wherein R^B is a hydrogen atom or lower alkyl), or -CH_2-; m is 1, 2, or 3;

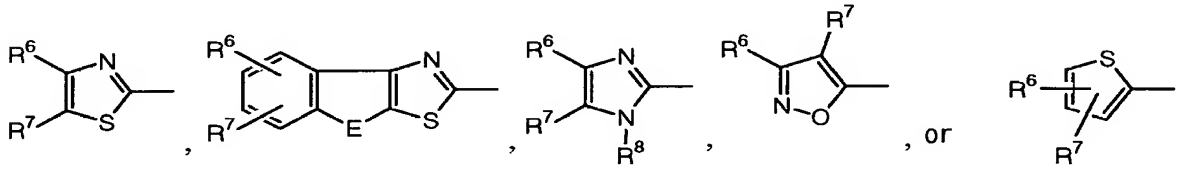
a broken line (---) represents the presence or absence of a bond;

provided that X^2 is not oxazole; and

X^2 is not thienyl when Y^2 is -$CONR^G$-$(CH_2)_{0-2}$-,

its prodrug, or their pharmaceutically acceptable salt, or solvate thereof.

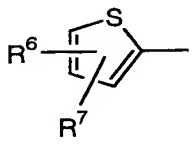
13. (Amendment) A compound of claim 12, wherein X^2 is a group represented by the formula:



wherein E is -$(CH_2)_{1-3}$-, -O-CH_2-, or -S-CH_2-; R^6 and R^7 are each independently a hydrogen atom, optionally substituted lower alkyl, carboxy, lower alkyloxycarbonyl, optionally substituted aminocarbonyl, optionally substituted thienyl, or optionally substituted phenyl; R^8 is a hydrogen atom or lower alkyl,

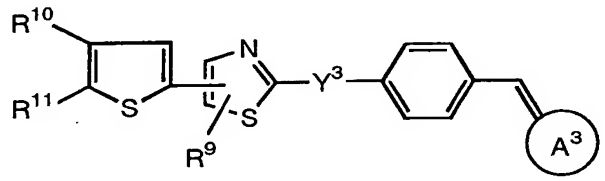
provided that both R^6 and R^7 are not hydrogen atoms at the same time when X^2 is

(1st Amendment)



its prodrug, or their pharmaceutically acceptable salt, or solvate thereof.

(1st Amendment)



(III-B)

wherein R^9, R^{10}, R^{11}, Y^3, and A^3 ring are as defined in claim 19,

its prodrug, or their pharmaceutically acceptable salt, or solvate thereof.

21. A pharmaceutical composition containing a compound of any one of claims 12 to 20 as an active ingredient.

22. A pharmaceutical composition which contains as an active ingredient a compound of any one of claims 12 to 20 for exhibiting thrombopoietin agonism.

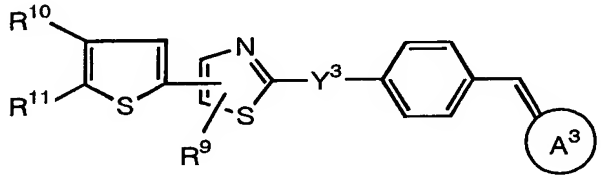
23. (Amendment) An agent for treating or preventing hemopathy accompanied with the unusual number of platelets which contains as the active ingredient a compound of any one of claims 12 to 20.

24. A pharmaceutical composition containing as the active ingredient a compound of any one of claims 12 to 20, which is a platelet production modifier.

25. (Amendment) Use of a compound of any one of claims 12 to 20 for preparation of a pharmaceutical composition for treating hemopathy accompanied with the unusual number of platelets.

26. (Amendment) A method for treating hemopathy accompanied with the unusual number of platelets of a mammal, including a human, which comprises administration to said mammal of a compound of any one of claims 12 to 20 in a pharmaceutically effective amount.

(2nd Amendment)



(III-B)

wherein R^9, R^{10}, R^{11}, Y^3, and A^3 ring are as defined in claim 19,

its prodrug, or their pharmaceutically acceptable salt, or solvate thereof.

21. A pharmaceutical composition containing a compound of any one of claims 12 to 20 as an active ingredient.

22. A pharmaceutical composition which contains as an active ingredient a compound of any one of claims 12 to 20 for exhibiting thrombopoietin agonism.

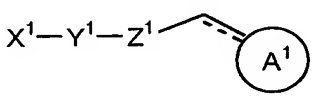
23. An agent for treating or preventing hemopathy accompanied with the unusual number of platelets which contains as the active ingredient a compound of any one of claims 12 to 20.

24. A pharmaceutical composition containing as the active ingredient a compound of any one of claims 12 to 20, which is a platelet production modifier.

25. Use of a compound of any one of claims 12 to 20 for preparation of a pharmaceutical composition for treating hemopathy accompanied with the unusual number of platelets.

26. A method for treating hemopathy accompanied with the unusual number of platelets of a mammal, including a human, which comprises administration to said mammal of a compound of any one of claims 12 to 20 in a pharmaceutically effective amount.

27. (Addition) A composition as thrombopoietin receptor agonist which contains as an active ingredient a compound of the formula (I):



(I)

(2nd Amendment)

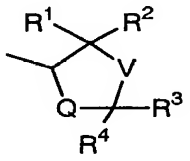
wherein X^1 is optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, or optionally substituted non-aromatic heterocyclic group;

Y^1 is $-NR^ACO-(CH_2)_{0-2}-$, $-NR^ACO-(CH_2)_{0-2}-W-$, $-NR^ACO-CH=CH-$, $-W-(CH_2)_{1-5}-NR^ACO-(CH_2)-$, $-W-(CH_2)_{1-5}-CONR^A-(CH_2)_{0-2}-$, $-CONR^A-(CH_2)_{0-2}-$, $-(CH_2)_{0-5}-NR^A-SO_2-(CH_2)_{0-5}-$, $-(CH_2)_{0-5}-SO_2-NR^A-(CH_2)_{0-5}-$, $-NR^A-(CH_2)_{0-2}-$, $-NR^A-CO-NR^A-$, $-NR^A-CS-NR^A-$, $-N=C(-SR^A)-NR^A-$, $-NR^ACSNR^ACO-$, $-N=C(-SR^A)-NR^ACO-$, $-NR^A-(CH_2)_{1-2}-NR^A-CO-$, $-NR^ACONR^ANR^FCO-$, or $-N=C(-NR^AR^A)-NR^A-CO-$,

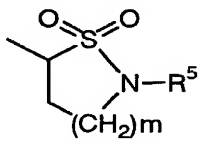
wherein R^A is each independently a hydrogen atom, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl, R^F is a hydrogen atom or optionally substituted aryl, W is an oxygen atom or a sulfur atom;

Z^1 is optionally substituted arylene, optionally substituted heteroarylene, optionally substituted non-aromatic heterocycle-diyl, or optionally substituted cycloalkyl-diyl;

A^1 is a ring represented by the formula:



or



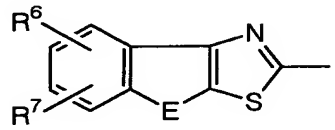
wherein R^1 and R^2 are both hydrogen atoms or taken together may form an oxygen atom or a sulfur atom; R^3 and R^4 are both hydrogen atoms or taken together may form an oxygen atom or a sulfur atom; R^5 is a hydrogen atom or lower alkyl; Q and V are each independently -O-, -S-, $-NR^B-$ (wherein R^B is a hydrogen atom or lower alkyl), or $-CH_2-$; m is 1, 2, or 3;

a broken line (---) represents the presence or absence of a bond,

its prodrug, or their pharmaceutically acceptable salt, or solvate thereof.

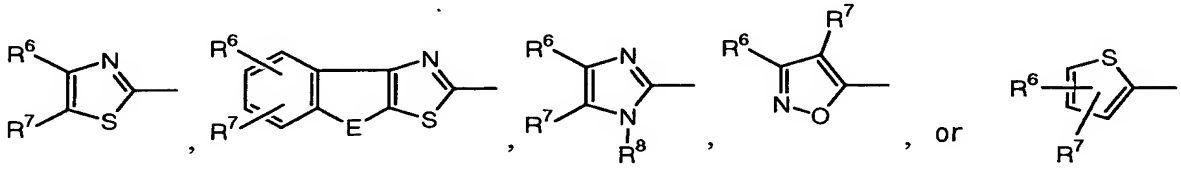
(2nd Amendment)

28. (Addition) A composition as thrombopoietin receptor agonist of claim 27, wherein X^1 is optionally substituted 5-member heteroaryl or a group represented by the formula:



wherein E is $-(CH_2)_{1-3}-$, $-O-CH_2-$, or $-S-CH_2-$; R^6 and R^7 are each independently a hydrogen atom, optionally substituted lower alkyl, carboxy, lower alkyloxycarbonyl, optionally substituted aminocarbonyl, optionally substituted thienyl, or optionally substituted phenyl.

29. (Addition) A composition as thrombopoietin receptor agonist of claim 27, wherein X^1 is a group represented by the formula:



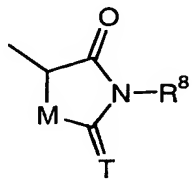
wherein E is $-(CH_2)_{1-3}-$, $-O-CH_2-$, or $-S-CH_2-$; R^6 and R^7 are each independently a hydrogen atom, optionally substituted lower alkyl, carboxy, lower alkyloxycarbonyl, optionally substituted aminocarbonyl, optionally substituted thienyl, or optionally substituted phenyl; R^8 is a hydrogen atom or lower alkyl.

30. (Addition) A composition as thrombopoietin receptor agonist of claims 27 to 29, wherein Y^1 is $-NHCO-$, $-CONH-$, $-NHCH_2-$, or $-NHSO_2-$.

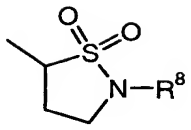
31. (Addition) A composition as thrombopoietin receptor agonist of claims 27 to 30, wherein Z^1 is 1,4-phenylene.

32. (Addition) A composition as thrombopoietin receptor agonist of claims 27 to 31, wherein A^1 is a ring represented by the formula:

(2nd Amendment)



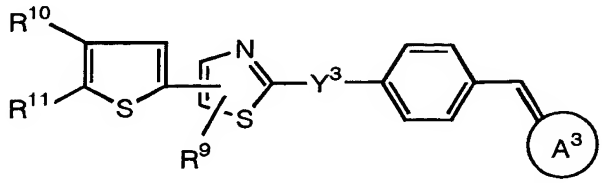
or



wherein R^8 is a hydrogen atom or lower alkyl; M is -S-, -O-, -N(R^c)-, or -CH_2- (wherein R^c is a hydrogen atom or lower alkyl); T is an oxygen atom or a sulfur atom.

33. (Addition) A composition as thrombopoietin receptor agonist of claims 27 to 32, wherein the broken line represents the presence of a bond.

(3rd Amendment)



(III-B)

wherein R^9, R^{10}, R^{11}, Y^3, and A^3 ring are as defined in claim 19,

its prodrug, or their pharmaceutically acceptable salt, or solvate thereof.

21. A pharmaceutical composition containing a compound of any one of claims 12 to 20 as an active ingredient.

22. A pharmaceutical composition which contains as an active ingredient a compound of any one of claims 12 to 20 for exhibiting thrombopoietin agonism.

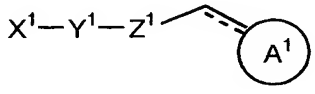
23. An agent for treating or preventing hemopathy accompanied with the unusual number of platelets which contains as the active ingredient a compound of any one of claims 12 to 20.

24. A pharmaceutical composition containing as the active ingredient a compound of any one of claims 12 to 20, which is a platelet production modifier.

25. Use of a compound of any one of claims 12 to 20 for preparation of a pharmaceutical composition for treating hemopathy accompanied with the unusual number of platelets.

26. A method for treating hemopathy accompanied with the unusual number of platelets of a mammal, including a human, which comprises administration to said mammal of a compound of any one of claims 12 to 20 in a pharmaceutically effective amount.

27. (Amendment) A composition as thrombopoietin receptor agonist which contains as an active ingredient a compound of the formula (I):



(I)

(3rd Amendment)

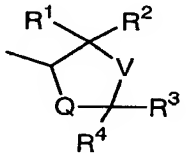
wherein X^1 is optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, or optionally substituted non-aromatic heterocyclic group;

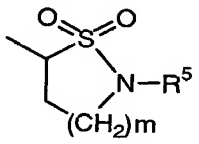
Y^1 is $-NR^ACO-(CH_2)_{0-2}-$, $-NR^ACO-(CH_2)_{0-2}-W-$, $-NR^ACO-CH=CH-$, $-W-(CH_2)_{1-5}-NR^ACO-(CH_2)_{0-2}-$, $-W-(CH_2)_{1-5}-CONR^A-(CH_2)_{0-2}-$, $-CONR^A-(CH_2)_{0-2}-$, $-(CH_2)_{0-5}-NR^A-SO_2-(CH_2)_{0-5}-$, $-(CH_2)_{0-5}-SO_2-NR^A-(CH_2)_{0-5}-$, $-NR^A-(CH_2)_{0-2}-$, $-NR^A-CO-NR^A-$, $-NR^A-CS-NR^A-$, $-N=C(-SR^A)-NR^A-$, $-NR^ACSNR^ACO-$, $-N=C(-SR^A)-NR^ACO-$, $-NR^A-(CH_2)_{1-2}-NR^A-CO-$, $-NR^ACONR^ANR^FCO-$, or $-N=C(-NR^AR^A)-NR^A-CO-$,

wherein R^A is each independently a hydrogen atom, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl, R^F is a hydrogen atom or optionally substituted aryl, W is an oxygen atom or a sulfur atom;

Z^1 is optionally substituted arylene, optionally substituted heteroarylene, optionally substituted non-aromatic heterocycle-diyl, or optionally substituted cycloalkyl-diyl;

A^1 is a ring represented by the formula:



or


wherein R^1 and R^2 are both hydrogen atoms or taken together may form an oxygen atom or a sulfur atom; R^3 and R^4 are both hydrogen atoms or taken together may form an oxygen atom or a sulfur atom; R^5 is a hydrogen atom or lower alkyl; Q and V are each independently -O-, -S-, $-NR^B-$ (wherein R^B is a hydrogen atom or lower alkyl), or $-CH_2-$; m is 1, 2, or 3;

a broken line (---) represents the presence or absence of a bond,

its prodrug, or their pharmaceutically acceptable salt, or solvate thereof.